Exo-to-*endo* nitrogen transposition in saturated rings

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Abstract: Biologically active molecules are often comprised of ring structures that precisely position functional groups to enable target-specific interactions. The iterative permutation of these structural arrangements is central to the modern drug discovery process, necessitating *de novo* synthesis to access isomeric compounds with distinct biological properties. However, methods to interconvert saturated ring systems remains limited. We report a general method for the peripheral-to-core nitrogen internalization of amino cycloalkanols to access *N*-heterocycles of various oxidation states. In this process, an excited-state iridium chromophore and weak Brønsted base cooperatively promote the endergonic redox isomerization of cyclic amino alcohols to linear amine-containing products that undergo *in situ* cyclization. This strategy enables the expansion, contraction, and carbon-to-nitrogen substitution of cyclic amino alcohols, providing access to structurally distinct heterocyclic scaffolds.

Introduction: Saturated ring systems are common structural elements in biologically active molecules, orienting functional groups in specific spatial and stereochemical arrangements that enable selective binding to target receptors. The direct transposition of peripheral functional groups into ring structures represents a potentially powerful approach to access isomeric structures with altered biological profiles. For example, replacement of an amine-substituted carbocycle with the corresponding *N*-heterocycle in a recently reported JAK1 inhibitor was shown to drastically alter drug metabolism and pharmacokinetics (DMPK) while improving target potency (Fig. 1A) (*1*). Accordingly, the development of synthetic methods to directly transform amino-carbocycles to *N*-heterocycles would be an enabling tool for structural diversification (Fig. 1B) (*2, 3*). While significant progress has been made in the skeletal editing of planar sp^2-hybridized (hetero)arenes to access distinct heterocyclic scaffolds, analogous reactions for the diversification of saturated ring systems are rare (*4*). Seeking to address this limitation, we report here a general strategy to transform cyclic amino alcohols to a range of structurally distinct nitrogen-containing heterocycles of varying ring sizes and oxidation states (Fig. 1C).

Vicinal amino alcohols are structural motifs that can be readily obtained from common starting materials, including cyclic alkenes, epoxides, amines, alcohols, and more (*5-9*). We anticipated that proton-coupled electron transfer (PCET) activation may enable the *exo*-to-*endo* nitrogen transposition of these amino cycloalkanols and serve as a non-canonical entry point for the synthesis of nitrogen-containing heterocycles. In 2019, we reported the redox-neutral isomerization of unactivated cyclic alcohols to linear carbonyl compounds. In these reactions, an excited-state oxidant together with a weak Brønsted base simultaneously remove a proton and electron from the O–H bond of an alcohol substrate (*10*). The high energy alkoxy radical intermediate undergoes C–C cleavage *via* β-scission to afford carbonyl-containing products and an alkyl radical which can either be reduced by a thiol co-catalyst or further functionalized. Extending this work, we envisaged that PCET activation of cyclic 1,2-amino alcohols would provide linear amino carbonyl products that are amenable to downstream modification (*11*). While both alcohols and amine derivatives readily participate in PCET activation, the reversible nature of excited-state PCET together with the low propensity for unstrained *N*-centered radicals to undergo β-scission suggests the C–C bond cleavage will proceed *via* the alkoxy radical and therefore be highly regioselective (*12*). Subsequent reduction of the resulting α-amino radical by hydrogen-atom transfer (HAT) with a thiol co-catalyst furnishes the linear amino-carbonyl intermediate in a net redox-neutral isomerization process. The chemically differentiated end-groups of this linear intermediate enable polarity-matched *in situ* cyclization to a common iminium intermediate (see Fig. 1C) that can be directly transformed to a number of distinct *N*-heterocycles in various oxidation states.

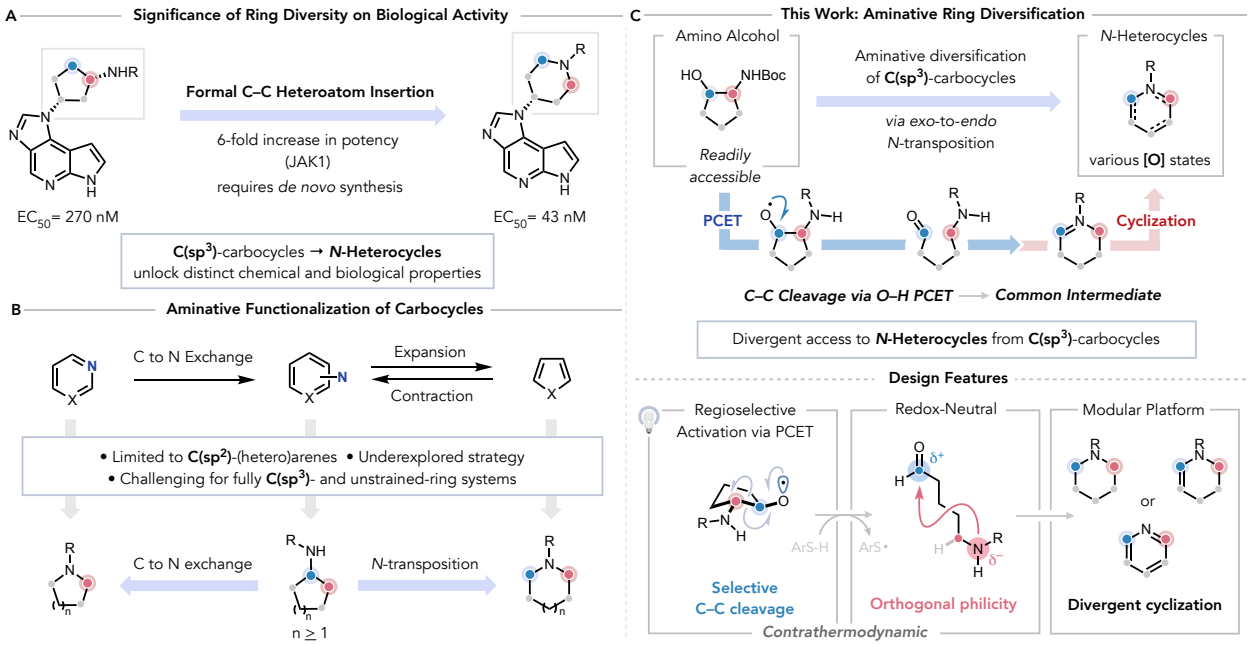
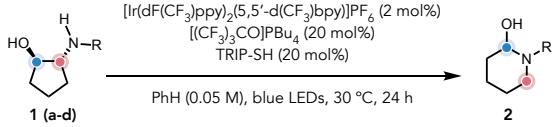


Fig. 1. Reaction Development (**A**) Amination of carbocycles emulates molecular optimization process in drug discovery. (**B**) Contemporary strategies for the aminative modification of ring systems. (**C**) PCET-enabled aminative ring diversification of amino cycloalkanols and design features.

Results and Discussion:

With this design in mind, we began our optimization with *tert*-butyloxycarbonyl (Boc)-protected *trans*-1,2-aminocyclopentanol (**1a**, Table 1). A promising lead result was observed using 2 mol% [Ir(dF(CF_3)ppy)$_2$(5,5'-d(CF_3)bpy)]PF_6 photocatalyst, 20 mol% tetrabutylphosphonium nonafluoro-*tert*-butyl alkoxide base, and 20 mol% of 2,4,6-triisopropylbenzenethiol (TRIP-SH) in benzene, providing 48% of the cleavage product **2** upon blue light irradiation (456 nm) for 24 hours at 30 ºC. We note that although ^{1}H NMR spectroscopic analysis of the crude reaction mixtures revealed that the isomerization product **2** existed exclusively as the cyclic hemiaminal conformer, the majority of substrates evaluated in this study provided linear ring-opened products. Using the free amine or replacement of the Boc-protecting group with other acyl protecting groups resulted in diminished yields of the cleavage product (entries 2-4), and further studies identified benzene as an optimal solvent for this reaction. We ultimately found that addition of 40 mol% of 2,4,6-triisopropylbenzenedisulfide and prolonging the reaction time to 30 hours led to an improved yield of 75% (entry 5) (*13, 14*). Altering the base identity was detrimental to product generation (entry 6-8). The absence of photocatalyst or light provided no product, and trace yields were observed in the absence of the Brønsted base or thiol co-catalyst (entries 9-11). In analogy to our prior work (*10*), computational evaluation of the thermochemistry for the isomerization of the methyl carbamate form of **1a** revealed that the linear amino carbonyl products were higher in energy than the amino cycloalkanol starting materials (ΔG° = +5.2 kcal/mol at 298 K, CBS-QB3) (*15*).

With these optimized isomerization conditions in hand, we next explored conditions for the *in situ* cyclization of the amino-carbonyl intermediate formed following the PCET event (see Fig. S1. for the proposed mechanism). Our initial efforts focused on the reductive cyclization of these intermediates to access saturated *N*-heterocycles. We surveyed standard reductive amination conditions which led to mixtures of the desired heterocycle and carbonyl reduction products. However, we found that after Boc-deprotection with trifluoroacetic acid (TFA), the crude amino-carbonyl intermediates underwent intramolecular condensation to form a cyclic imine intermediate when treated with sodium carbonate and molecular sieves in hexafluoroisopropanol (HFIP). This cyclic imine was subsequently reduced by the addition of sodium borohydride to furnish the saturated heterocycle. We note that HFIP proved uniquely effective for promoting imine formation at room temperature (*16*). While these conditions proved general and effective for the reductive expansion of most substrates, in some cases the use of sodium acetate and sodium triacetoxyborohydide (STAB-H) was necessary for efficient cyclization. Notably, this two-step process was conducted in a single pot with only one rotary evaporation in between stages, followed by sequential addition of reagents.



Entry	R	Deviation from Standard Conditions	**2** (%)
		N-Protecting Group	
1	Boc (**1a**)	–	48
2	Cbz (**1b**)	–	31
3	Ac (**1c**)	–	27
4	H (**1d**)	–	0
5	Boc (**1a**)	–	75[a]
		Base Identity	
6	Boc	$[(PhO)_2P(O)O]NBu_4$ (20 mol%)	<10[a]
7	Boc	$[(PhO)_2P(O)O]PBu_4$ (20 mol%)	<10[a]
8	Boc	2,4,6-collidine (2 equiv)	0[a]
		Controls	
9	Boc	No photocatalyst or light	0[a]
10	Boc	No thiol	<5
11	Boc	No base	<5[a]

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Table 1. Reaction Optimization. Reactions were run on a 0.05 mmol scale. Yields were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture with piperonal as an internal standard. [a]40 mol% $(TRIP\text{-}S)_2$ and the reaction was irradiated for 30 h.

Having identified optimal conditions for the conversion of amino cycloalkanols to saturated *N*-heterocycles, we explored the synthetic scope of the aminative ring expansion. A wide range of substituted five- and six-membered amino cycloalkanols successfully underwent aminative insertion to furnish the structurally distinct piperidine and azepane heterocycles, respectively (Fig. 2A). The relative stereochemistry between the amine and alcohol groups had minimal effect on the overall efficiency of the transformation, with *cis*- and *trans*-aminocyclopentanol providing the corresponding piperidine in 53% and 52% yields, respectively (**2b**). 2-Substituted amino cycloalkanols possessing alkyl or phenyl substituents cleanly underwent aminative ring expansion to the corresponding 2-substituted-piperidines in good yields (**3-6**). A 2-pyridyl-substituted amino cyclopentanol was converted to the anabasine analog **7** in 48% yield. The aminative diversification of cyclohexane-derived amino alcohols to saturated azepane cores was next evaluated. Similar to the 5-membered substrates, the conversion of the 6-membered amino alcohols possessing alkyl substituents to 2-substituted azepanes proceeded in moderate yields (**8-10**). Electron-rich and -deficient arene containing amino alcohols were also efficient substrates (**11-14**). Additionally, although our attempts achieve a one-pot asymmetric reductive ring-expansion only provided trace amounts of cyclization product, we note that an iridium-catalyzed asymmetric reductive cyclization of the linear redox-isomerization products **4b** and **11b** has recently been reported (*17*). To this end, the enantiopure 2-phenylpiperidine **(+)-4** and 2-phenylazepane **(+)-11** could readily be accessed in two steps from the corresponding amino cycloalkanol (see Fig. 3A).

We next applied this methodology towards the diversification of terpene-derived amino alcohols, accessed from the corresponding terpenes. The 3-carene and α-pinene derived aminocyclohexanols underwent aminative expansion to the corresponding 4-azabicyclo[5.1.0]octane (**15**) and 3-azabicyclo[4.1.1]octane (**16**) in 46% and 52% yield, respectively. The tricyclic amine **17** was accessed from the cedrene derived amino alcohol in 49% yield. Additionally, the camphor-derived amino alcohol was efficiently expanded to the 3-azabicyclo[3.2.1]octane (**18**) in 57% yield.

Azasteroids have garnered significant attention due to their promising biological profiles (*18*). We next applied the reductive aminative ring expansion protocol to complex steroid-derived amino cycloalkanols to access this valuable class of natural product derivatives. We were pleased to see that the amino alcohols derived from steroids bearing alkenes on either the A-, B-, or D-rings underwent facile aminative ring expansion. For instance, the amino alcohol derived from $\Delta_{2,3}$-cholestene provided A-ring-modified azasteroid **19** in 73% yield. The expansion of dehydro-*epi*-androsterone and *trans*-androstene derivatives provided the corresponding B-ring-modified piperidine and D-ring-modified azepane azasteroids in 39% and 50% yield, respectively (**20-21**).

The ring contraction of cyclic amines is an attractive strategy for the modification of existing heterocyclic scaffolds (*19-22*). We recognized that this strategy could be extended to the contraction of endocyclic amino alcohols

(Fig. 2B). To this end, hydroxy-piperidines and -azepanes underwent PCET-enabled ring contraction to access the corresponding *N*-alkyl-pyrrolidines and -piperidines, respectively, in a formal endo-to-exocyclic extrusion of a carbon atom from the heterocyclic core.

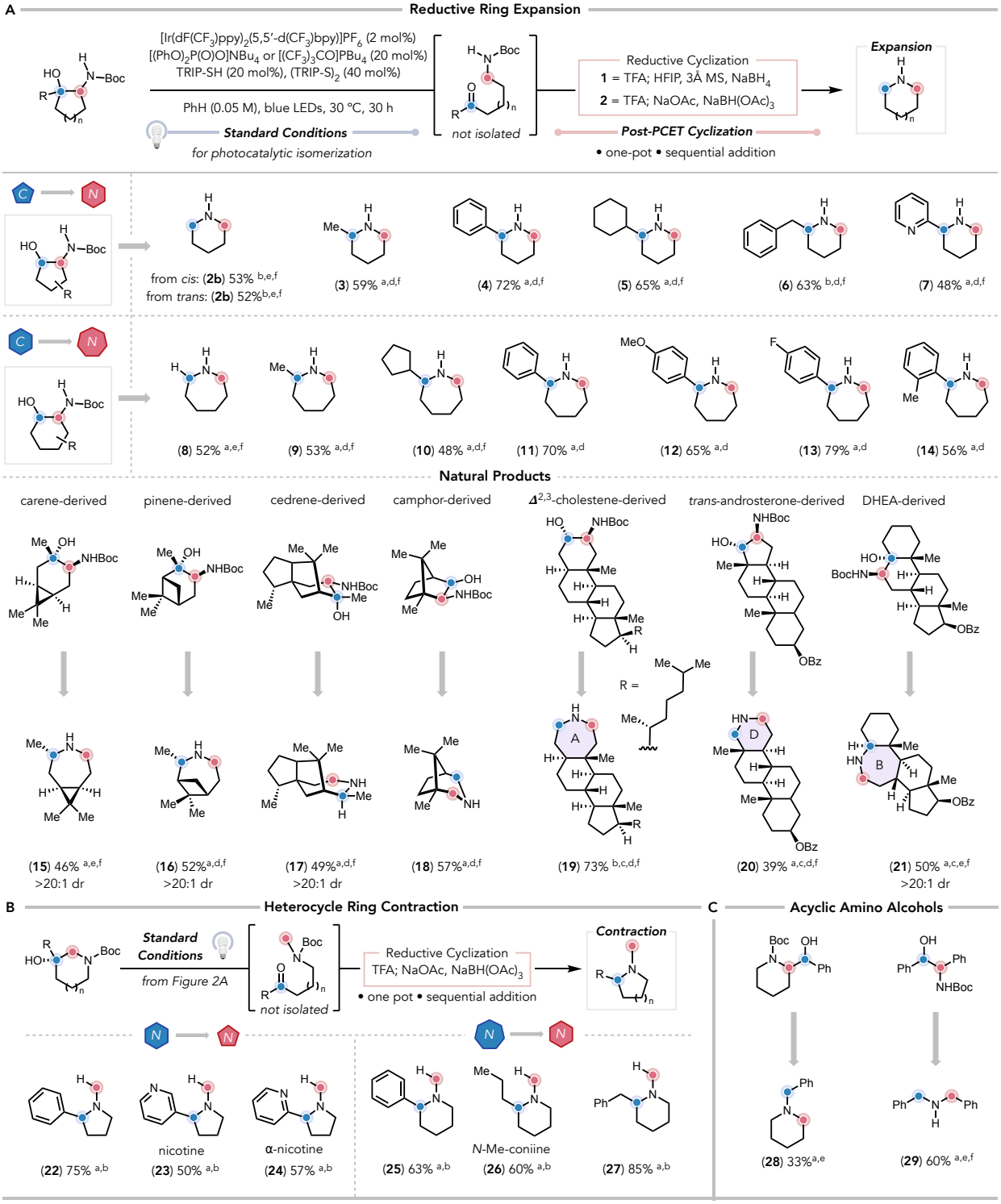

Fig. 2. Reaction Scope. Reactions were run at 0.2 mmol scale and no purification of intermediates were performed prior to cyclization. Yields are for isolated material after purification unless otherwise noted and are the average of two experiments. (**A**) PCET-enabled amino cycloalkanol aminative ring expansion to saturated *N*-heterocycles. (**B**) PCET-ring contraction of *N*-heterocycles. (**C**) Recombinative reductive amination of acyclic substrates. [a][(PhO)$_2$P(O)O]NBu$_4$ was used as base. [b][(CF$_3$)$_3$CO]PBu$_4$ was used as base. [c]0.1 M concentration of benzene solvent.

[d]Cyclization condition 1 was used. [e]Cyclization condition 2 was used. [f]Secondary amine products were Boc-protected prior to isolation.

Subjection of 3-hydroxy-3-phenylpiperidine to the standard reaction conditions provided the contracted *N*-methyl-2-phenyl-pyrrolidine (**22**) in 75% yield. Both 2- and 3-pyridyl substituted hydroxypiperidines were efficiently contracted to afford nicotine (**23**) and α-nicotine (**24**) in 50% and 57% yield, respectively. 3-Hydroxyazepanes were also effective substrates in the PCET ring contraction (**25-27**). Additionally, we demonstrate that this methodology were used for the transposition of acyclic amino alcohols *via* recombinative reductive amination (**28-29**). In these reactions, the carbonyl and amine fragments generated after C–C bond cleavage undergo intermolecular reductive amination to afford the structurally reconfigured amine products.

The modularity of this PCET-enabled diversification strategy was next evaluated by varying the mode of *in situ* cyclization. We began with desaturative expansion to access synthetically useful tetrahydropyridines (Fig. 3B) (*23*). Unsubstituted and alkyl-substituted 5- and 6-membered amino cycloalkanols were converted to the corresponding cyclic ene-carbamates (**30-33**) at elevated temperature with 20 mol% *p*-toluenesulfonic acid (PTSA) and a desiccant. Notably, the post-PCET intermediates possessing alkyl ketones and aldehyde moieties underwent cyclization to ene-carbamates, whereas the aryl ketones provided only trace amounts of product.

Although carbon-to-nitrogen substitution reactions of (hetero)arenes have recently been reported, analogous transformations of fully sp^3-hybridized carbocycles remain limited (*24-26*). To this end, we identified that the desaturative ring expansion and ring contraction protocols could be conducted iteratively to facilitate the formal carbon-to-nitrogen atom replacement in amino-cycloalkanols to access *N*-heterocycles with net retention of ring size (Fig. 3C). In the first stage, the desaturative ring expansion of a 6-membered cyclic amino alcohol afforded the ene-carbamate. This substrate was then subjected to a hydroboration-oxidation sequence to access the corresponding hydroxy-azepane **34**. Notably, this two-step sequence represents a formal constitutional isomerization of the starting amino-alcohol substrate. In the final stage, subjecting **34** to the PCET-mediated ring contraction furnished piperidine **35** from the corresponding cyclohexyl substrate. Overall, this sequence involving the iterative migration of the amine group enables the conversion of saturated carbocycles to saturated *N*-heterocycles with retention of ring size and results in a formal carbon-to-nitrogen substitution reaction.

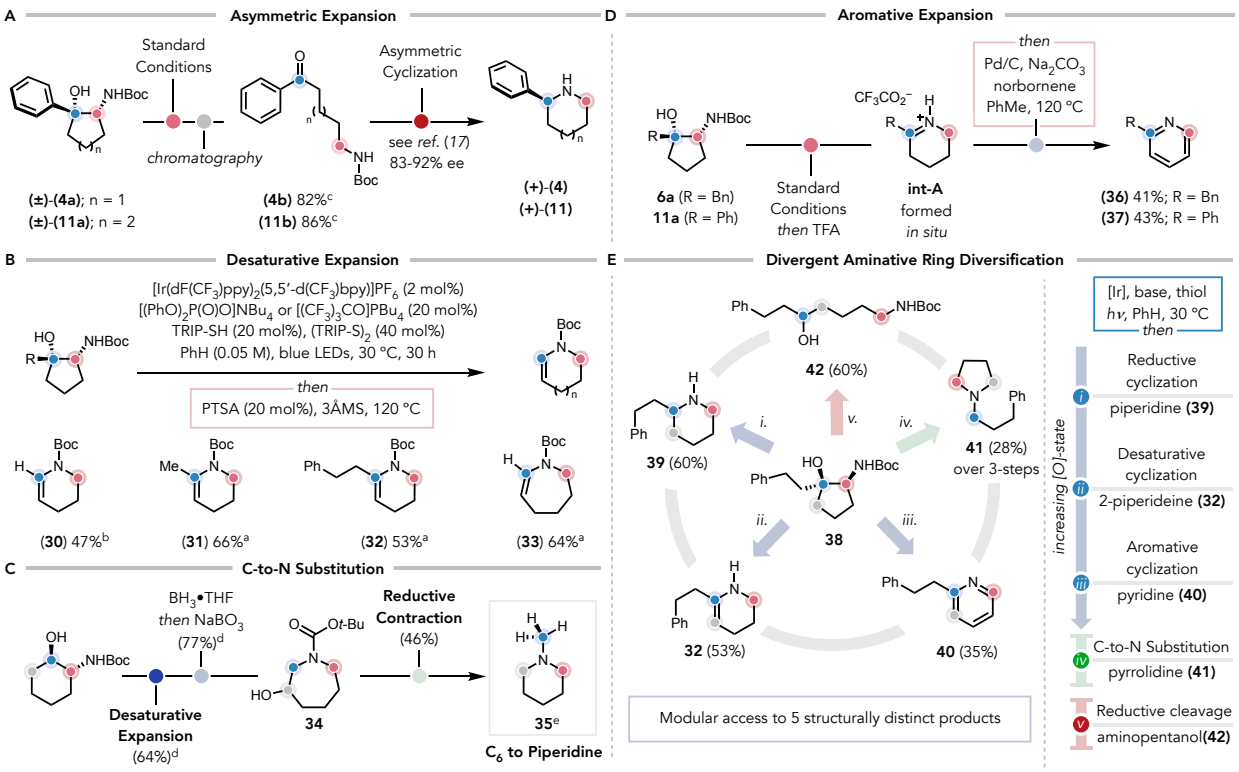

Fig. 3. Applications of a PCET-enabled diversification strategy. Reactions were run at 0.2 mmol scale and no purification of intermediates prior to cyclization were performed unless otherwise noted. Yields are for isolated material after purification unless otherwise noted and are the average of two experiments. (**A**) Two step synthesis of enantiopure *N*-heterocycles. (**B**) Desaturative ring-expansion of amino cycloalkanols. (**C**) C-to-N substitution *via* an

iterative amine migration sequence to access ring-size retentive *N*-heterocycles. (**D**) Aromative ring expansion of carbocycles to pyridines. (**E**) Divergent access to distinct scaffolds from a single carbocyclic input. [a][$(PhO)_2P(O)O]NBu_4$ was used as base. [b][$(CF_3)_3CO]PBu_4$ was used as base. [c]Yields were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture with piperonal as an internal standard. [d]Chromatographic purification was performed prior to the next step. [e]Yield was determined by GC analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard.

Heteroaromatic ring systems such as pyridines are one of the most common rings found in small molecule therapeutics (*27*); however, transformations that access these important ring structures from existing carbocycles are limited (*28*). Here we apply this strategy to the conversion of amino cyclopentanols to ring-expanded pyridines by subjecting the post-PCET intermediate to *in situ* oxidative aromatization conditions (Fig. 3D) We were pleased to find that transfer dehydrogenation of the iminium (**int-A**), generated from acid-mediated deprotection-condensation, with palladium-on-carbon and norbornene as the hydrogen acceptor promotes the conversion of cyclopentyl substrates **6a** and **11a** to 2-benzylpyridine (**36**) and 2-phenylpyridine (**37**) in 41% and 43% yield, respectively (*29*).

The ability to transform a single carbocyclic core to various structurally distinct scaffolds is a powerful strategy for efficiently exploring novel chemical space (*30*). We next demonstrate that this aminative diversification strategy can enable the parallel construction of several structurally and electronically distinct nitrogen-containing scaffolds from a single carbocyclic starting material (Fig. 3E). Starting from 5-membered carbocyclic amino alcohol **38**, reductive aminative ring expansion leads to the corresponding saturated piperidine (**39**) in 60% yield. Higher oxidation state heterocycles tetrahydropyridine (**32**), and pyridine (**40**) were synthesized from **38** through the desaturative and aromative cyclization conditions, in 53% and 35% yields, respectively. Additionally, the three-step iterative amine migration sequence was performed to access pyrrolidine (**41**) in a net carbon-to-nitrogen substitution in 28% yield over three-steps. Lastly, the formal C–C bond hydrogenation of the cyclic amino alcohol to the corresponding linear amino alcohol (**42**) in 70% yield *via in situ* reduction of the amino-carbonyl intermediate with $NaBH_4$ following the PCET event. Taken together, this approach enables access to several distinct cyclic and linear scaffolds in parallel from a single carbocyclic input and underscores the applicability of this PCET- mediated transformation for the diversification of saturated carbocycles.

Conclusion: We have developed a modular strategy for the diversification of saturated rings that provides a new retrosynthetic tactic for *N*-heterocycle synthesis. This *exo*-to-*endo* nitrogen transposition approach provides non-canonical access to a diverse array of nitrogen-containing heterocycles, proceeds with precise redox control, and is uniquely enabled by the mild, catalytic, and redox-neutral bond activation of amino cycloalkanols. The ability to efficiently access diverse heterocyclic scaffolds from commonly encountered C(sp^3)-carbocyclic starting materials positions this strategy for the diversification of existing molecular architectures and can streamline the design and synthesis of complex *N*-heterocyclic compounds.

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Acknowledgments: We thank Prof. Teshik Yoon, Cade MacAllister, and Matthieu Maciejewski for helpful discussions regarding a related study prior to publication. We additionally thank Suhong Kim, Jose Roque, Andrew Feng, Diego Granados and Emily Du for helpful discussions.

Funding: Support for this work was provided by the National Institute of General Medical Sciences of the National Institutes of Health (NIGMS R35 GM134893) (R.R.K.). D.Q.T. thanks the National Institute of General Medical Sciences for financial support through a postdoctoral fellowship (F32GM151832).

Author contributions: Both authors contributed to the conceptualization of the project, the planning of experiments, and interpretation of results. R.R.K. directed the research. D.Q.T. conducted the experiments. D.Q.T. and R.R.K. wrote the manuscript.

Competing interests: The authors declare no competing interests.

Data and materials availability: All experimental data are available in the main text or the supplementary materials.

Supplementary Materials

Materials and Methods

Figs. S1 to S8

Tables S1 to S4

References (*31*-*64*)